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NEW VARIETIES AND SPECIES OF MALARIA PLASMODIA *

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Although it has been nearly twenty-four years since Laveran announced his discovery of the parasites concerned in the etiology of the malarial fevers, and although an immense amount of work has been expended on the study of these parasites in the endeavor to arrive at a classification of them that can be accepted by all observers, we are still far from achieving that happy result, as is readily evident if one compares the classifications given by the authors of the most recent works on the subject. While most authorities agree that there are at least three species of malaria plasmodia, they do not all agree as regards nomenclature, and Laveran still adheres to the belief in the unity of all malaria plasmodia occurring in man, regarding the so-called species as variations in a single pleomorphous species.

In view of the evidence that has accumulated regarding the morphology, life cycle and relation to disease of the plasmodia of malaria, I believe, with most investigators, that several species of malaria plasmodia exist. The marked differences in the morphology of the species generally accepted, which are constant; the length of their cycle in man; the symptoms produced by their presence and the periodicity of the occurrence of these symptoms, all point to the conclusion that we are dealing with different species, while the fact that each plasmodium reproduces its kind when experimentally inoculated into man and with that reproduction gives rise to the characteristic clinical symptoms commonly produced by the species inoculated, makes the evidence in favor of distinct species practically conclusive. When to these evidences is added the fact that certain species of mosquitoes can only transmit certain species of the plasmodia, the evidence would appear to be incontrovertible.

As a matter of fact, Laveran is practically alone in his advocacy of the unity of the human malaria plasmodia, for the consensus of opinion among protozoologists is in favor of the plurality of species. While this is so, there is still considerable disagreement regarding the number of species which should be recognized and the classifications

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of Grassi and Feletti (1890), Mannaberg (1899), Sacharoff (1896), Lühe (1900), Schaudinn (1902), Doflein (1911) and others differ somewhat in this respect, although the majority recognize at least three species, the tertian, quartan and estivo-autumnal plasmodia. The names given these species also vary with different authorities, but if the generally accepted rules of nomenclature be followed, the tertian plasmodium must be called *Plasmodium vivax* (Grassi and Feletti), the quartan, *Plasmodium malariae* (Marchiafava and Bignami), and the estivo-autumnal, *Plasmodium falciparum* (Welch). While, as has been stated, nearly all authorities admit the existence of the three species mentioned, there is still considerable discussion regarding the existence of still other species, especially of species of the estivo-autumnal plasmodium. By many observers the plasmodia encountered in the malarial fevers generally known as estivo-autumnal are divided into two species, the subtertian or tertian, and the quotidian, while by some the latter is divided into a pigmented and unpigmented quotidian plasmodium.

During the past sixteen years I have had the opportunity of studying the plasmodia in thousands of cases of estivo-autumnal malaria and have reached the conclusion that two distinct species of plasmodia are concerned in the etiology of these forms of malarial fever, one sporulating in twenty-four hours, the other in forty-eight hours. These two species of plasmodia were first described by Marchiafava and Bignami, and there is no doubt in my mind that they can be distinguished morphologically and that, in uncomplicated instances of infection, they each produce a characteristic form of malarial fever. In previous communications (1901, 1909) I have described in detail the morphology and life cycle of these plasmodia and the symptoms produced by infection with them, and further research has only convinced me of the truth of Marchiafava and Bignami's classification of the estivo-autumnal plasmodia. Later (1909a) I proposed the name *Plasmodium falciparum quotidianum* for the quotidian species of the estivo-autumnal plasmodium, considering it a subspecies of the subtertian or tertian estivo-autumnal plasmodium, or *Plasmodium falciparum*. Accordingly, at the present time, I believe that there are four well-defined species of malaria plasmodia, namely, *Plasmodium vivax*, the tertian; *Plasmodium malariae*, the quartan; *Plasmodium falciparum*, the subtertian or tertian estivo-autumnal, and *Plasmodium falciparum quotidianum*, the quotidian estivo-autumnal.

Recently there have appeared contributions by two different observers describing new varieties or species of the malaria plasmodia. In view of the interest which must attach to the discovery of any new forms of these parasites in man, and as I believe that I have observed plasmodia similar in every respect to those described in the contributions mentioned, it has seemed of importance to place my observations on record together with some critical comments regarding the subject. In April, 1914, in the *Proceedings of the Royal Society* and in the *Annals of Tropical Medicine and Parasitology,* J. W. W. Stephens (1914, 1914a) described what he considered a new species of malaria plasmodia of man, while in May, 1914, in the *Bulletin de la Société de Pathologie Exotique,* Ahmed Emin described (1914) a plasmodium which he regarded as a variety of *Plasmodium vivax,* the benign tertian plasmodium. Stephens has named the plasmodium observed by himself *Plasmodium tenue,* while Emin has named his *Plasmodium vivax* variety *minuta.* Both contributions are well illustrated by presumably correct drawings of the plasmodia described, else I would not feel justified in discussing the parasites, not having seen the actual preparations containing them. However, as I have repeatedly observed plasmodia answering in every detail to those described and illustrated in the papers referred to, I feel no hesitation in recording my observations in confirmation of the existence of these forms, although I cannot agree with all that is noted regarding the so-called *Plasmodium tenue* in so far as its classification as a new species is concerned. The plasmodium described by Ahmed Emin will first be considered.

PLASMODIUM VIVAX VARIETY MINUTA

This plasmodium was observed in the blood of pilgrims in the hospital at Camaran, an island in the Red Sea, about 30 miles from Hodeidah. Emin describes the plasmodium as resembling the benign tertian plasmodium (*Plasmodium vivax*), but differing from it principally in its smaller size, lack of enlargement of the infected erythrocyte, and smaller number of spores or *merozoites.* The pigment present in the plasmodium is fine and resembles that in *Plasmodium vivax.* At the time of sporulation the plasmodium almost entirely fills the erythrocyte, which is not enlarged, and from four to ten merozoites are produced by the division of the parasite. Ameboid motility is slight as compared with that of *Plasmodium vivax.* Multiple infection of the erythrocyte was not infrequently observed, and one of the drawings shows an erythrocyte containing as many as five schizonts in the "ring" stage of development. Emin believes that while there are marked differences between this plasmodium and *Plasmodium vivax,* it resembles the latter to such an extent that it should properly be regarded as a variety rather than a new species, and proposes the name *Plasmodium vivax* variety *minuta.*

In 1899 and 1900, while studying the malaria plasmodia observed in the blood of our soldiers returning from the Philippines, at the

U. S. Army General Hospital, Presidio of San Francisco, Cal., I observed a plasmodium in the blood of six patients answering to the description of the variety *minuta* of Emin, and my observations were published in the Report of the Surgeon-General of the Army (Craig, 1900). Emin's description of his plasmodium answers almost exactly to that of the plasmodia observed in these cases, and his drawings are accurate reproductions of the plasmodia that I observed. Since that time I have noted the same plasmodium in regions where only tertian infections are present, and I am in agreement with him in considering it to be a variety of *Plasmodium vivax*. The following is my original description of this plasmodium, as published in the Surgeon-General's Report:

"In studying the blood of soldiers returning from the Philippines and suffering from malaria, I have noticed in several cases a peculiar form of the malarial parasite which I have classified in reporting on the cases as a tertian parasite, but which presents so many differences from the ordinary tertian parasite as to indicate that it is a distinct variety of the plasmodium.

"I have invariably observed it in the blood of patients having tertian paroxysms and always in large numbers. All stages of the parasite have been observed, from the hyaline disks to the segmenting bodies. It appears first as a very highly refractive circular hyaline disk within the erythrocyte, having a sharply cut outline and no ameboid motion. The absence of ameboid motion differentiates it from all other young forms of the malarial parasites. The hyaline disk is about one-fourth the size of the infected corpuscle, which is normal in size and appearance.

"In a few hours the hyaline disk has grown to about one-half the size of the corpuscle which contains it and has become pigmented. The pigment exactly resembles that found in the ordinary tertian parasite, being finely granular and motile and distributed unequally throughout the parasite. The parasite is circular in shape and devoid of ameboid motion. The border of the parasite is very sharply defined and the protoplasm very refractive and sometimes finely granular. The infected corpuscle is unaltered in size and color and is not crenated or shrunken.

"In about thirty-eight to forty hours the parasite has nearly filled the corpuscle containing it, and the amount of pigment has increased. The parasite is circular in shape and presents the same refractive protoplasm and sharply cut border; the pigment is sluggishly motile, reddish in color and in the shape of fine granules. The infected corpuscle is normal in size and color.

"I have not as yet observed the presegmenting forms in the blood, but have seen several segmenting forms. These are much smaller than the ordinary tertian segmenting forms, and the greatest number of segments observed has been ten. The segments are oval in shape or perfectly round, sharply cut and refractive. The pigment is usually collected in a solid reddish-brown mass at the center of the segmenting parasite and is immotile."

After giving the differential points between this parasite and the other species of malaria plasmodia, consisting chiefly in size, shape, ameboid motility, number of merozoites and character and arrangement of the pigment, I call attention to the fact that "The differentiation of this parasite from the quartan organism is really much more difficult than is the case with the tertian or estivo-autumnal plasmodia. Indeed, I mistook them for quartan parasites until the clinical histories of the cases and certain peculiarities of the parasites caused me to study them more carefully." They differ from *Plasmodium malariae* in the lesser degree of ameboid motility, in the larger amount of and more finely granular pigment, and in having a human life cycle of forty-eight hours instead of seventy-two hours. In conclusion, I state:

"I believe that this parasite is either a distinct variety of the malaria plasmodia or that it is a tertian parasite which has acquired the characteristics described through some unknown condition of environment acting on the development of the organism."

It will be noted that in my original description I mention that ameboid motility was absent in this plasmodium, but further observations have proved that it is present, but very much less pronounced than in *Plasmodium vivax*. The round form of this plasmodium is well illustrated in Emin's drawings and the number of merozoites mentioned by him, four to ten, agrees exactly with my own observations, the largest number I have ever noted being ten. My original description was based on the living organisms, but later observations on specimens stained with Wright's modification of the Romanowsky stain confirm Emin's description of the stained plasmodium. The chromatin stains very intensely and tends to collect near the periphery of the plasmodium after the latter is half grown and just before sporulation, while the pigment at this time collects at or near the center of the plasmodium, the merozoites frequently being arranged regularly around the mass of pigment, giving the plasmodium the typical daisy or "marguerite" appearance, often spoken of as being characteristic of the sporulating forms of *Plasmodium malariae*.

Emin states that he could not be sure whether Schuffner's dots occurred in the infected erythrocyte, but in my experience they do occur, but much less frequently than in the case of erythrocytes infected with *Plasmodium vivax,* and the dots are smaller and less in number. I believe that those who have reported Schuffner's dots as occurring in erythrocytes infected with the quartan plasmodium (*Plasmodium malariae*) have really been observing the variety *minuta* of *Plasmodium vivax,* for it is with the quartan plasmodium that this plasmodium is most apt to be confused. Indeed, the resemblance of this variety of the tertian plasmodium to the quartan, so far as morphology goes, is much greater than it is to the tertian plasmodium, but the fact that the parasite is found only in cases having a tertian periodicity, together with the character of the pigment and its arrangement, definitely separates it from *Plasmodium malariae,* and demonstrates that it is closely related to the tertian plasmodium. In the stained preparations the fine pigment, the characteristic arrangement of the chromatin and the absence of "band forms" serve to distinguish this variety of *Plasmodium vivax* from *Plasmodium malariae,* but unless one is well acquainted with the morphology of the latter plasmodium this variety of the tertian parasite will almost certainly be confused with it.

The occurrence of all stages of development in the peripheral blood is sufficient to differentiate this plasmodium from either *Plasmodium falciparum* or *Plasmodium falciparum quotidianum,* while the large size of the organism and its general morphology definitely proves that it does not belong to either of these species.

From my own observations, which are confirmed by those of Emin, I believe that this plasmodium should be considered a variety of *Plasmodium vivax,* and that it should be known by the name given it by Emin, that is, *Plasmodium vivax* variety *minuta.* I do not believe that the evidence is sufficient to prove that it is entitled to specific rank.

PLASMODIUM TENUE

In two identical contributions published separately, Stephens (1914, 1914a) describes what he considers a new species of malaria plasmodium. This so-called species is described from the parasites observed in a single blood-slide sent Stephens by Major Kenrick, I.M.S., from Pachmari, Central Provinces, India. Both of the contributions are illustrated with the same drawings and demonstrate conclusively that the plasmodia present in this slide are all in practically the same stage of development, so that the species is described from only one stage of development, and that an early stage, before the development of pigment. This parasite Stephens has named *Plasmodium tenue,* and he states that he believes that it has affinities with the simple tertian plasmodium and with *Plasmodium canis* of the dog. rather than with the malignant tertian parasite.

Basing his deductions entirely on the stained preparation, Stephens considers the distinguishing features of this species to be extreme ameboid activity, scanty cytoplasm, and an amount of nuclear chromatin out of proportion to the volume of the parasite. The extreme ameboid activity is evidenced by the marked variations in the shape of the parasite, ring forms being rare, while the vast majority of the organisms present long, thin processes stretching across the infected erythrocyte, frequently multiple in number. The small amount of cytoplasm is contained within these filamentous processes. The nuclear chromatin appears out of proportion to the volume of the plasmodium, occurring in the form of rods, strands, forked masses, patches, etc. The chromatin is situated in the protoplasmic processes either as strands, rods or angular masses situated at the junction of the two processes. Stephens says: "Abundance of and marked irregularity in the distribution of the chromatin masses are characteristic of this parasite."

Stephens considers that this plasmodium differs from the malignant tertian plasmodium (*Plasmodium falciparum*) in possessing greater ameboid activity and in the abundance and irregularity of the nuclear chromatin, and from the simple tertian plasmodium (*Plasmodium vivax*) in being smaller, having more delicate ameboid processes, a larger amount of and more marked irregularity in the distribution of the chromatin, and in the rarity of typical "ring" forms.

From the description of this organism given by Stephens and the drawings which accompany the description, it is, to say the least, extremely doubtful if this parasite can be accepted as a new species of malaria plasmodium. Even though it differed from the known species to a much greater extent than is described, it would be entirely unjustifiable to describe it as a new species from the morphology of the parasite during only a small portion of the life cycle and from the organisms observed in a single stained blood-smear. The morphological details on which the species is based are inadequate to establish the species, especially as the plasmodium is undoubtedly in that stage of development, the young unpigmented stage, in which a differential diagnosis from *Plasmodium vivax* would be most difficult. As a matter of fact, Stephens states that he is in doubt as to whether Schuffner's dots occur in the infected erythrocyte, but admits finding one infected erythrocyte which was enlarged and showed Schuffner's dots. Regarding the morphology of the plasmodium observed in this erythrocyte, Stephens says: "Although I could detect no pigment in this parasite I was not otherwise able to distinguish it from a simple tertian parasite."

Admitting, as I believe nearly every protozoologist will, who has had an extensive experience with the plasmodia of human malaria, that the classification of this organism as a new species is not justified, owing to the fact that practically only one stage of development has been observed and that the morphological characteristics are not sufficient to base a species on, the question remains as to the exact position of this plasmodium which appears to possess some peculiarities not usually described for the well-known species of human plasmodia. From my own experience, I am convinced that all of the species of malaria plasmodia present at times, and from unknown or known causes, atypical generations, so far as morphology are concerned, and if specimens of blood containing such plasmodia be studied to the exclusion of others from the same infection, one is most apt to regard these plasmodia as varieties or new species. Time and again I have been on the point of describing such atypical plasmodia as new species and have only hesitated because of previous experience with similar forms. In many of the patients showing these atypical plasmodia continued observation has demonstrated that the atypical forms were replaced by typical examples of one of the well-known species, while in other instances a minute examination of the preparations would show that, while the atypical plasmodia were the most numerous, typical parasites of one of the recognized species did occur, though perhaps in very small numbers.

As regards the parasite described by Stephens as *Plasmodium tenue,* I may say that I have several times encountered exactly similar parasites, so far as I can determine from his description and drawings, in undoubted infections with *Plasmodium vivax,* and for this reason I believe that Stephens' plasmodium is a rather atypical form of *Plasmodium vivax* in the unpigmented stage of development. As claimed by Stephens, the evidence of ameboid activity is pronounced, but no more so than is frequently observed in preparations of blood containing *Plasmodium vivax* at a corresponding stage of development, while the extreme delicacy of the cytoplasmic pseudopodia is frequently observed in tertian infections in which quinin has been administered in insufficient dosage to kill the plasmodia, but sufficient to produce a stimulation of ameboid activity and consequently a greater number of cytoplasmic processes. The amount of chromatin present in Stephens' plasmodium is greater than is usually observed at this stage of development, but not greater than I have observed in plasmodia in undoubted infections with *Plasmodium vivax,* in which the parasites were in the same stage of development. At this stage of development the infected erythrocyte is very frequently not enlarged in infections with the ordinary tertian plasmodium, so that the lack of enlargement of the erythrocyte is not a point in favor of a new species. As a matter of fact, the distortion in the shape of many of the infected erythrocytes, as shown in Stephens' drawings, is very characteristic of tertian infections, and the fact that the erythrocyte containing the single organism observed in a later stage of development (an organism which Stephens states he was unable to distinguish from *Plasmodium vivax* except for the absence of pigment) was enlarged and presented Schuffner's dots, is certainly good evidence that this parasite is a more or less atypical form of the ordinary tertian plasmodium, or *Plasmodium vivax*.

The reasons underlying the production of morphologically atypical generations of malaria plasmodia are obscure, but I am convinced that insufficient dosage with quinin, and perhaps with other drugs, often leads to the production of such plasmodia and that these plasmodia may retain for several generations morphological abnormalities produced by adverse agencies, either physical or chemical. We know that in the case of *Entamoeba histolytica* the character of the nucleus is absolutely changed by the administration of drugs that produce a cessation of the acute symptoms of dysentery, and there is no reason why the same should not occur in the instance of the malaria plasmodia. So marked are the changes produced in the morphology of *Entamoeba histolytica* by either chemical or physical conditions leading to the cessation of acute symptoms that the form of the parasite occurring when the dysenteric symptoms abate was long regarded by the best protozoologists as a distinct species of entameba, and I believe that it is only reasonable to admit that the same influences may cause atypical generations of the malaria plasmodia.

In proof of this assertion I may state that I have followed infections in which the plasmodia were very atypical, being modified morphologically by the exhibition of small doses of quinin, and have seen a return to normal morphology when the drug was discontinued. One of the most common effects of quinin is a great stimulation in the ameboid activity of the malaria plasmodia and an apparent stimulation in the division of the chromatin, as evidenced by the presence of delicate pseudopodia containing an abnormal amount of chromatin during the early stages of development of the plasmodia. I would not wish to be understood as claiming that this is the explanation of the morphology of the parasite discussed in this instance, but I am satisfied that *Plasmodium tenue* is an atypical form of *Plasmodium vivax*. I have observed identical forms, so far as can be judged from the description and drawings, not once, but a considerable number of times, in supposedly untreated infections with *Plasmodium vivax*, and many times in infections with this plasmodium after the exhibition of doses of quinin insufficient to kill the plasmodia.

However, whether or not this parasite is identical with *Plasmodium vivax*, it cannot be accepted as a new species until the morphology of the parasites during the entire human life cycle at least is studied, for the only claim it now has to specific rank is the presence of slight differences in morphology during a very limited portion of the human life cycle, that is, the early unpigmented stages of development when such differences are commonly observed even in the well-recognized species of plasmodia.

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